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Urea: a comprehensive review of the clinical literature

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Abstract:
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Methods: A PubMed search was conducted using the term “urea” combined with “skin,” “ichthyosis,” “psoriasis,” “xerosis,” “emollient,” “onychomycosis,” “dermatitis,” and “avulsion.” A total of 81 publications met inclusion criteria and were evaluated. Treatment indication(s), test agents, number of subjects, treatment protocols, results, and side effects were recorded.

Results: Effective treatment with urea has been reported for the following conditions: ichthyosis, xerosis, atopic dermatitis/eczema, contact dermatitis, radiation induced dermatitis, psoriasis/ seborrheic dermatitis, onychomycosis, tinea pedis, keratosis, pruritus, and dystrophic nails. Furthermore, urea has been used with other medications as a penetration enhancing agent. Mild

irritation is the most common adverse event, proving urea to be a safe and tolerable topical drug without systemic toxicity.

Discussion/Conclusion: Urea is a safe, effective dermatologic therapy with wide-ranging clinical utility and minimal, non-systemic side effects. In order to optimize patient care, dermatologists should be well informed with regards to urea's indications and efficacy.

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Review

Urea: a comprehensive review of the clinical literature

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Abstract

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Discussion/Conclusion: Urea is a safe, effective dermatologic therapy with wide-ranging clinical utility and minimal, non-systemic side effects. In order to optimize patient care, dermatologists should be well informed with regards to urea's indications and efficacy.

Keywords: urea, ichthyosis, xerosis, dermatitis, eczema, psoriasis, onychomycosis, pruritus, tinea pedis, avulsion

Introduction

The efficacy and safety of urea in the treatment of skin diseases has been reported for more than a century. Urea is an organic compound chemically structured as a carbonyl group attached to two amine residues. Physiologically, urea plays an important role in the metabolism and excretion of nitrogen-containing products. Since it was first described, a substantial and evolving literature has been established describing its therapeutic role in the treatment of a myriad of dermatologic conditions. Urea has been employed as a proteolytic agent for wound debridement as well as a topical bacteriostatic agent in wounds [1–4]. As far back as 1957, urea was viewed as an old, forgotten therapy when Kligman wrote, "it sometimes happens in the enthusiastic search for new therapeutic agents that some old stand-by has been overlooked, whose luster has worn off, but which none the less may have some useful application in moments when the miracle drugs falter. In the world of topical therapy, urea is such a drug [5]." We seek to reacquaint the medical community with the versatile clinical applications of urea by conducting a systematic review of the literature and summarizing published findings examining the efficacy of urea in treating dermatological conditions.

Current labeling of urea products includes indications for: (1) debridement and promotion of normal healing of hyperkeratotic surface lesions, particularly where healing is retarded by local infection, necrotic tissue, fibrinous or purulent debris, or eschar; (2) hyperkeratotic conditions such as dry, rough skin, dermatitis, psoriasis, xerosis, ichthyosis, eczema, keratosis, keratosis pilaris, keratosis palmaris, keratoderma, corns, and calluses; and (3) damaged, ingrown, and devitalized nails [6–12]. Although the mechanism of action of urea in skin is still unknown, studies suggest that the keratolytic and hydrating effects of topical urea is owing to breakage of hydrogen bonds in the stratum corneum, loosening epidermal keratin, and increasing water-binding sites [13]. Commercially available products containing prescription-grade urea concentrations are listed in Table 1 [6–12].

Table 1. Common commercially available prescription-grade urea products

Trade Name	Manufacturer*	Formulation	Vehicle
Carmol 40[6]	Doak Dermatologics	40% urea	Lotion, cream, or gel
U-Kera E[7]	TaroPharma	40% urea	Emollient cream
Urealac[8]	Hi-Tech Pharmacal Co.	50% urea	Topical suspension with lactic acid and salicyclic acid
Umecta[9]	Innocutis	40% urea	Emulsion, topical suspension, nail film suspension with applicator, or mousse
Vanamide[10]	Dermik Laboratories	40% urea	Cream
Kerol[11]	Doak Dermatologics	50% urea	Emulsion in zinc undecylenate and lactic acid
RE U40[12]	River's Edge	40% urea	Foam

*Manufacturer may differ

Methods

A PubMed search was conducted from inception to December 2011 using the term "urea" combined with "skin," "ichthyosis," "psoriasis," "xerosis," "emollient," "onychomycosis," "dermatitis," and "avulsion." The search results were reviewed for clinical trials, case reports, and case series examining the usage and efficacy of urea to treat dermatologic conditions. Additional articles were identified within the citations of qualifying publications that met inclusion criteria but were not returned in the initial PubMed search. The following information was recorded from these publications: the dermatologic condition being studied, test agents, number of subjects, treatment protocol, results, and side-effect profile.

Results

We obtained and reviewed 284 articles on urea therapies. Of these articles, 81 met our criteria of: 1) being a clinical study, case series or case report, 2) having urea as one of the experimental agents, and 3) describing a dermatological application for urea. The articles were then categorized by treatment for the following conditions: ichthyosis (11 articles), hydration of xerotic/healthy skin (14 articles), atopic dermatitis/eczema (10 articles), contact dermatitis (1 article), radiation-induced dermatitis (1 article), psoriasis/seborrheic dermatitis (14 articles), onychomycosis (5 articles), tinea pedis (4 articles), keratosis (13 articles), pruritus (1 article), dystrophic nails (2 articles), and penetration enhancement (5 articles). For each disease, we provide a summary of the literature highlighting the clinical efficacy and safety of urea treatment and a table detailing clinical trials or case reports for the more studied diseases.

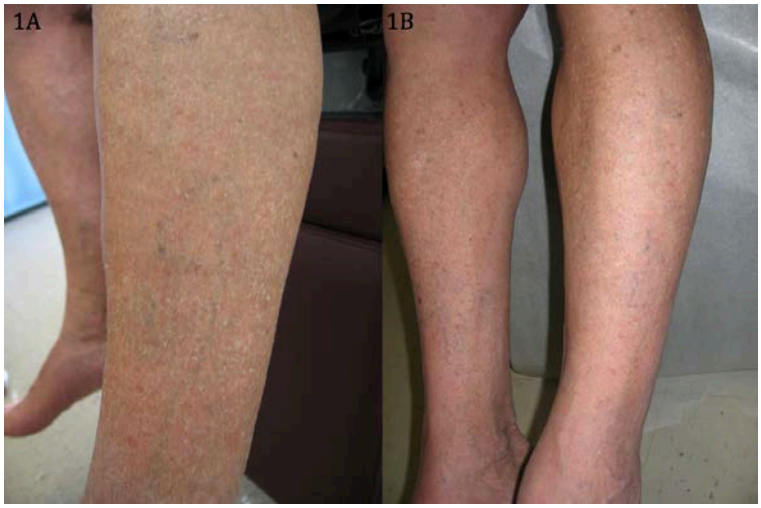

Figure 1. Patient with hyperkeratotic skin before (1A) and after (1B) treatment with 40% urea cream (U-Kera E [7]) for 12 days. Visible clinical improvement in skin texture is observed.

Ichthyosis

Ichthyosis refers to a heterogeneous subset of dermatologic conditions characterized by dry, thickened, and scaly skin. Although the most common form of ichthyosis is ichthyosis vulgaris, a variety of other disorders exhibit ichthyosiform scale. Topical urea has been shown to be an effective therapeutic option for patients with these disorders in a number of studies and expert opinions [14,15]. Urea (10%) was found to be equally or slightly more efficacious in controlling ichthyotic symptoms than 1% hydrocortisone cream [16], 2% salicylic acid ointment, and paraffin-based moisturizers [17]. The beneficial effects of urea on ichthyotic skin can be attributed to its water binding, barrier regenerating, desquamating, and anti-microbial properties [18,19]. Reports of only occasional mild burning or irritation associated with the use of topical urea preparations support an excellent safety profile. The studies are outlined in Table 2 [14–17,20–26].

Table 2. Clinical studies of urea in patients with ichthyosis

Disease Subtype	Test Agent	Comparison Agent	N	Study Design	Treatment Protocol	Results	Safety (N)*	Year	Reference
Bullosa of Siemens	10% urea lotion	5% lactic acid lotion	1	CT BL	BID x 8 weeks	Greater improvements with test agent based on global severity scale	No adverse effects reported	1998	[20]
Congenital	10% urea cream	Urea-free base cream	2	CT BL	QD x 4 weeks	Test agent produced “soft skin with visible changes like erythema”	No adverse effects reported	1968	[21]
Epidermolytic hyperkeratosis (EHK)	10% urea	None	1	CS	QD	90% improvement after 6 months	No adverse effects reported	2009	[22]
Keratitis-ichthyosis-deafness (KID) syndrome	5% and 10% urea cream	None	1	CR	QD x 2 weeks	Marked improvement in hyperkeratosis and palmoplantar keratoderma after 2 weeks of therapy	No adverse effects reported	2007	[23]
Laevis	10% urea cream	Urea-free base cream	2	CT BL	QD x 4 weeks	Test agent produced “normal appearance of skin”	No adverse effects reported	1968	[21]
Lamellar	5% urea emulsion	None	5	CS	BID x 6 weeks and 4 month maintenance	Improvement was observed in all treated areas	Mild burning, pruritus and irritation (2)	2011	[15]
Lamellar	10% urea lotion	5% lactic acid lotion	11	CT BL	BID x 8 weeks	Greater improvements with test agent based on global severity scale	No adverse effects reported	1998	[20]
Linearis	10% urea cream	Urea-free base cream	1	CT BL	Max 4 weeks	Test agent produced “normal appearance of skin”	No adverse effects reported	1968	[21]
Unspecified type with history of or present eczema	10% urea cream (pH 6 and 3)	None	30	CT BL	BID x 4 weeks	Both test agents improved skin conditions	Burning sensation (2) with pH	1975	[24]

							3 preparation		
Unspecified type with history of or present eczema	10% urea cream	1% hydrocortisone cream	19	CT BL	BID x 2 weeks	Improved response to urea (3), hydrocortisone (1), and no difference (12)	No adverse effects reported	1969	[16]
Vulgaris	10% urea lotion	Glycerol-based cream	27	CT BL	BID x 4 weeks	Urea reduced scaling, roughness, redness and cracking in comparison to control	No adverse effects reported	2011	[25]
Vulgaris	10% urea lotion	5% lactic acid lotion	34	CT BL	BID x 8 weeks	Greater improvements with test agent based on global severity scale	No adverse effects reported	1998	[20]
Vulgaris	10% urea cream	None	5	OL	QD x 2-4 weeks	Marked improvement in treated areas	No adverse effects reported	1989	[14]
Vulgaris	10% urea cream	Urea-free base cream, 0.1% retinoic acid	6	CT	BID x 3 weeks	Test agent increased the water uptake by 100% compared to the control	No adverse effects reported	1973	[26]
Vulgaris	10% urea cream	2% salicylic acid ointment, paraffin	37	CT BL	BID x 2 weeks	Test agent showed greater clinical improvement	No adverse effects reported	1972	[17]
Vulgaris	10% urea cream	Urea-free base cream	2	CT BL	QD x 4 weeks	Test agent produced “soft skin with visible changes like erythema”	No adverse effects reported	1968	[21]
X-linked recessive	10% urea lotion	5% lactic acid lotion	6	CT BL	BID x 8 weeks	Greater improvements with test agent based on global severity scale	No adverse effects reported	1998	[20]
X-linked recessive	10% urea cream	Urea-free base cream, 0.1% retinoic acid	8	CT	BID x 3 weeks	Test agent increased the water uptake by 100% compared to the control	No adverse effects reported	1973	[26]
X-linked recessive	10% urea cream	2% salicylic acid ointment, paraffin	47	CT BL	BID x 2 weeks	Test agent showed greater clinical improvement	No adverse effects reported	1972	[17]

Abbreviations: CT - controlled trial, OL - open label, CS – case series, CR – case report, BL – bilateral comparison (test versus control), QD – once daily, BID – twice daily, TID – thrice daily

*Safety profile is reported only for test agents containing urea.

Xerosis

Numerous randomized controlled trials support the use of urea in the treatment of xerosis. Typically administered in concentrations less than or equal to 10%, the hydrating properties of urea can offer clinical benefit to patients with xerosis [27,28]. In many studies, transepidermal water loss (TEWL) is used as the primary parameter for assessing skin hydration. Several experiments have shown that urea can reduce TEWL in both xerotic and healthy skin [29]. Cream was shown to be a slightly better vehicle than foam in one study [30]. Studies on the hydrating effects of urea in patients with either xerotic or healthy skin are outlined in Table 3[14,16,29,31–33] and Table 4[30,34–40], respectively.

Table 3. Clinical studies of the hydrating effects of urea in patients with xerosis

Test Agent	Comparison Agent	N	Study design	Treatment Protocol	Results	Safety (N)*	Year	Reference
10% urea lotion with dexpanthenol	None	15**	OL	BID x 4 weeks	Test agent improved skin dryness and pruritus	Mild burning (1)	2011	[31]
15% urea	Untreated	12	CT BL	BID x 2 weeks	Test agent reduced TEWL in all individuals	No adverse effects reported	2009	[29]

40% urea	12% ammonium lactate	25	CT BL	QD x 2 weeks	Test agent improved roughness, thickness and dryness in less time	No adverse effects reported	2002	[32]
10% urea cream	12% ammonium lactate	36	CT BL	BID x 3 weeks	Test agent lowered TEWL and dryness	No adverse effects reported	1998	[33]
10% urea	None	10	OL	QD x 2-4 weeks.	Test agent reduced chapping and scaling of skin	No adverse effects reported	1989	[14]
10% urea cream	1% hydrocortisone cream	14	CT BL	BID x 2 weeks	Improvement with: test (4), comparison (2), and no difference (7)	No adverse effects reported	1969	[16]

Abbreviations: CT - controlled trial, OL - open label, CS – case series, CR – case report, BL – bilateral comparison (test versus control), QD – once daily, BID – twice daily, TID – thrice daily, TEWL – transepidermal water loss
*Safety profile is reported only for test agents containing urea.
**Subjects were hemodialyzed patients with concurrent pruritus

Table 4. Clinical studies of the hydrating effects of urea in healthy subjects

Test Agent	Comparison Agent	N	Study design	Treatment Protocol	Results	Safety (N)*	Year	Reference
2-10% urea in cream or foam	Untreated	61	CT BL	3 separate studies conducted, varying protocols	Cream was better than foam in reducing TEWL and improving hydration	No adverse effects reported	2011	[30]
Urea with vitamins and ceramides	Urea alone	10	CT	QD x 2 weeks	Combination treatment superior in improving hydration and increasing gene expression of transglutamine-1, loricrin and filaggrin	No adverse effects reported	2008	[34]
Urea/NaCl emulsion	Urea alone	23	CT BL	BID x two weeks	Both agents equally effective in skin hydration	No adverse effects reported	2002	[35]
5% urea cream	5% hydrogenated canola oil	13	CT BL	BID x 2 weeks	Test agent decreased TEWL and reduced the irritant effects of sodium lauryl sulfate at day 14	No adverse effects reported	1997	[36]
10% urea emulsion	Various formulations	72	CT	BID or TID x max 20 days	TEWL and irritation to sodium lauryl sulfate was decreased after pre-treatment with test agent	No adverse effects reported	1996	[37]
2-4% urea cream	None	6	OL	Moisturizer x 1 hour followed by 0.25 – 24h exposure to SLS irritant	Test agent improves water retention by various parameters that quantified stratum corneum dynamic function	No adverse effects reported	1995	[38]
10% urea emulsion	Urea-free vehicle	54	CT	Heels treated TID x 3 days	Test agent increased the amount of cutaneous free water in the presence of high relative humidity	No adverse effects reported	1995	[39]
Moisturizers with varying urea content	Urea-free vehicle	26	CT	Measured epidermal hydration 3 hours after application	Test agent potently humidified skin and removed scale agent	No adverse effects reported	1992	[40]

Abbreviations: CT - controlled trial, OL - open label, CS – case series, CR – case report, BL – bilateral comparison (test versus control), QD – once daily, BID – twice daily, TID – thrice daily, TEWL – transepidermal water loss
*Safety profile is reported only for test agents containing urea.

Atopic Dermatitis/Eczema

Urea has been shown to improve stratum corneum hydration, water-binding capacity, and TEWL in eczematous skin [41]. The use of urea in atopic dermatitis has been studied most often using a concentration of 10% alone or in combination with 1% hydrocortisone [42]. Combination therapy with betamethasone-17-valerate has also been found to be clinically effective [43]. Nearly all studies demonstrated clinical improvement with urea treatment. Occasional stinging and burning were common side effects. The studies are outlined in Table 5 [21,24,41,43–48].

Table 5. Clinical studies of urea in patients with atopic dermatitis

Test Agent	Comparison Agent	N	Study design	Treatment Protocol	Results	*Safety (N)	Year	Reference
10% urea cream	None	10	OL	Observation performed 2 hours after application	Test agent improved stratum corneum hydration, water-binding capacity, and TEWL	No adverse effects reported	1989	[41]
10% urea + 1% hydrocortisone	0.1% hydrocortisone-17-butyrate	46	CT	QD x 3 weeks	No statistical difference between agents	No adverse effects reported	1979	[44]
10% urea cream, pH 6	10% urea cream, pH 3	30**	CT BL	BID x 4 weeks	Test agent showed statistically improved efficacy and acceptability	Burning sensation in more acidic preparation (13)	1975	[24]
1% hydrocortisone in 10% urea	0.1% betamethasone 17 valerate	36	CT BL	TID x 2-4 weeks	Comparable efficacy in majority of patients for both agents	No adverse effects reported	1974	[45]
1% hydrocortisone in 10% urea	0.1% betamethasone 17 valerate	49	CT BL	QD x 2 weeks	No statistical difference between two agents	No adverse effects reported	1974	[46]
1% hydrocortisone in 10% urea	Acidic 1% hydrocortisone in 10% urea	41	CT BL	QD x 2 weeks	Non-acidic test agent was clinically superior to acidic preparation	No adverse effects reported	1974	[46]
10% urea +1% hydrocortisone cream	1% hydrocortisone cream	48	CT BL	TID up to 5 weeks	Test agent was clinically superior to hydrocortisone alone.	Stinging (23)	1973	[47]
1% hydrocortisone in 10% urea	0.1% betamethasone-17-valerate	50	CT BL	BID x 2-3 weeks	Test agent was less effective than comparison agent.	Excoriated skin (6)	1973	[48]
10% urea + 0.1% betamethasone-17-valerate	0.1% betamethasone-17-valerate alone	42	CT BL	QD x 10 days	Test agent showed greater improvement with normal skin restored in 18 patients	No adverse effects reported	1971	[43]
10% urea +1% hydrocortisone cream	Base cream	12	CT BL	QD up to 4 weeks	All patients treated with test agent developed softer/smoother skin	Burning/itching (1)	1968	[21]

Abbreviations: CT - controlled trial, OL - open label, CS – case series, CR – case report, BL – bilateral comparison (test versus control), QD – daily, BID – twice daily, TID – thrice daily, TEWL – transepidermal water loss
*Safety profile is only reported for test agents containing urea.
**Subjects were diagnosed with ichthyosis with a history of or present atopic dermatitis

Contact Dermatitis

One randomized controlled double-blinded study investigated the use of 1% hydrocortisone/10% urea/1% lactic acid (Calmuril-Hydrocortisone) cream compared to 0.05% betamethasone-17, 21-dipropionate (Diproderm) cream in 100 subjects diagnosed with contact dermatitis. Subjects were asked to rub the cream twice daily for seven days onto the affected skin; clinical assessment was performed on the first, third, and seventh days. Diproderm cream was significantly more effective than the urea-containing Calmuril-Hydrocortisone cream. Smarting was reported less frequently in patients treated with Diproderm (n=2) than Calmuril-Hydrocortisone (n=7). The authors caution to avoid long-term treatment with steroid-containing creams to minimize the risk of dermatrophia [49].

Radiation-Induced Dermatitis

There are limited studies investigating the use of urea in the treatment of radiation-induced dermatitis. One controlled trial investigated the effects of a lotion containing 3% urea, polidocanol, and hyaluronic acid applied three times per day in 98 subjects with breast cancer to prevent acute radiation dermatitis. The control group of 174 subjects received a less intensive standard therapy. Treatment was started two to three weeks prior to radiation therapy and throughout the radiation treatment. The proportion of subjects who did not develop radiation dermatitis was significantly higher in the group that used the lotion containing urea (27.6% compared to 15.5%). The authors concluded that patients with breast cancer who received intensive use of

the lotion were half as likely to develop radiation dermatitis during radiotherapy. Only two patients reported adverse reactions during the study, one with follicular keratosis and another with an allergic reaction [50].

Psoriasis/Seborrheic Dermatitis

In psoriasis, urea improves stratum corneum hydration, water-binding capacity, and TEWL [41]. The majority of studies of urea in psoriasis were performed as part of combination therapies with dithranol. In one study, 10% urea monotherapy was found to be effective with few side effects [51]. Urea (40%) with 1% bifonazole was found to be effective in the treatment of scalp seborrheic dermatitis and scalp psoriasis [52]. Reported side effects were limited to occasional stinging and burning. An unwanted side effect that occurs when urea is combined with dithranol is the staining of the skin and clothes to a purplish brown color. The studies are outlined in Table 6 [21,41,51–62].

Table 6. Clinical studies of urea in patients with psoriasis

Test Agent	Comparison Agent	N	Study design	Treatment Protocol	Results	Safety (N)*	Year	Reference
40% urea plus 1% bifonazole ointment	None	71	OL	Multi-month protocol	73.2% of patients improved after 2 weeks	No adverse reactions reported	2000	[54]
10% urea ointment	Vehicle alone or no treatment	10	CT BL	TID x 2 weeks	Urea reduced scaling, erythema and induration and increased epidermal hydration	No adverse reactions reported	1996	[51]
10% urea cream	None	10	OL	Observed 2h after application	Significant increase in water content and decrease in TEWL and hygroscopicity	No adverse reactions reported	1989	[41]
12% urea and 12% sodium chloride	Cream base	30	CT BL	BID x 3 weeks	No statistical difference between treatments	Burning sensation (2)	1985	[55]
12% urea and 12% sodium chloride	Cream base	40	CT BL	BID x 1 week	Urea cream had statistically significant improvement on scaling	No adverse reactions reported	1985	[56]
0.1% dithranol plus 17% urea	None	41	OL	BID x 6 weeks	Clinical improvement from baseline was 64% and 77% at two centers	Mild irritation reported; 3 patients withdrew due to dithranol-related soreness	1983	[57]
0.2% dithranol in 17% urea	0.1% dithranol in 17% urea	20	CT BL	BID x 6 weeks	0.2% dithranol + urea cream had improved reduction in erythema and scaling	2 patients withdrew due to severe irritation and burning	1982	[52]
0.1% dithranol in 17% urea cream base	0.1% dithranol in Lassar's paste	35	CT BL	QD x 4 weeks	No statistical difference between two treatments	Less inflammation, stinging, itching, discoloration with test agent at 4 weeks	1981	[58]
0.1% dithranol in 17% urea	Salicylic acid 2% in strong coal tar solution 10%	40	CT BL	BID x 6 weeks	No statistical difference between two treatments	Transient irritation and skin coloration (2)	1981	[59]
0.1% dithranol in a 17% urea base	None	20	OL	QD until clearance	Mean time to clearance was 8.8 days; rapid reduction in both induration and scaling within first few days of treatment	Staining of hair (2) and irritation in post auricular skin (3)	1980	[60]

0.1% dithranol plus 17% urea	0.1% betamethasone-17-valerate	23	CT BL	BID x 6 weeks	No statistical difference between two treatments	Skin discoloration	1979	[53]
0.1% dithranol in a 17% urea base	17% urea base	8	CT BL	BID x 3 weeks	54% vs. 26% clinical improvement of scaling with combination therapy vs. urea monotherapy, respectively	Stinging and pain (7) and skin discoloration (1)	1978	[61]
0.1% dithranol plus 17% urea	0.05% clobetasol propionate	43	CT	QD x 3 weeks	Urea combination produced 80% of the clinical effect of comparison agent	Stinging and skin staining	1978	[62]
10% urea cream	Urea-free base or fluocinolone acetonide ointment	5	CT BL	QD x 5 days to 4 weeks	Urea cream resulted in soft and pliable skin but erythema was unchanged	Itching or burning (1)	1968	[21]

Abbreviations: CT - controlled trial, OL - open label, CS – case series, CR – case report, BL – bilateral comparison (test versus control), QD – daily, BID – twice daily, TID – thrice daily, TEWL – transepidermal water loss
*Safety profile is only reported for test agents containing urea.

Onychomycosis

Combination therapies consisting of urea with a variety of antifungal agents have been found to partially cure onychomycosis in some patients. By softening the nail bed, urea facilitates greater penetration of antifungal medications. Pretreating nails with a preparation of urea and hydrogen peroxide plus thioglycolic acid has been found to increase ungula flux of terbinafine ten fold. Moreover, this pretreatment has been found to augment the fungicidal activity of ciclopirox and amorolfine [63]. Combination therapy of urea with topical bifonazole or topical fluconazole has been shown to be clinically superior to monotherapy [64,65]. One study showed that 40% urea applied twice daily causes chemical avulsion of nails in patients with onychomycosis, facilitating the removal of fungal keratin without anesthesia or bleeding [66]. The studies are outlined in Table 7 [64–68].

Table 7. Clinical studies of urea in patients with onychomycosis

Test Agent	Comparison Agent	N	Study design	Treatment Protocol	Results	Safety (N)*	Year	Reference
Fluconazole 1% with urea 40%	Fluconazole 1%	70	CT	QD x 6-12 months	Test agent produced higher rate of negative cultures and clinical improvement	Redness and tingling at application site (1)	2011	[65]
Solution of 1% fluconazole and 20% urea	None	13	OL	QD x 12-18 months	Test agent showed complete clinical cure (4) and good clinical response (8)	No adverse reactions reported	2005	[67]
40% Urea nail lacquer	None	10	OL	BID x 1-2 weeks	Test agent showed keratinolysis of nail plate, ease of affected nail removal and lack of unpleasant smell	No adverse reactions reported	2002	[66]
40% urea\1% bifonazole cream	None	70	OL	QD x 3 months	Overall 62.5% improvement rate and 50% mycological cure rate	Erosions (2) with one discontinuation	1998	[64]
40% urea/1% bifonazole ointment with oral griseofulvin	40% urea/1% bifonazole ointment or ointment alone	22	CT	QD x 6 months	Test agent produced superior response compared to either monotherapy	No adverse reactions reported	1992	[68]

Abbreviations: CT - controlled trial, OL - open label, CS – case series, CR – case report, BL – bilateral comparison (test versus control), QD – daily, BID – twice daily, TID – thrice daily
*Safety profile is only reported for test agents containing urea.

Tinea Pedis

Urea can decrease the fissuring and scaling associated with dermatophytoses [69]. Although urea monotherapy has been reported to have antimicrobial properties, it has also been studied in combination with antifungal creams and appears to enhance efficacy over topical antifungal monotherapy, with only rare instances of self-limited irritation. A study compared 1% lanoconazole with or without 10% urea in 43 patients with hyperkeratotic type tinea pedis. Therapy was applied daily after a bath for 12 weeks. The authors observed a 96% improvement in the combined therapy group compared to 70% improvement in the lanoconazole monotherapy group. No adverse events were reported [70]. Urea in combination with topical bifonazole[64], ciclopirox[71], or butenafine hydrochloride[72] was also found to be effective with minimal adverse effects.

Emollient/Keratolytic

Various *in vitro* and *in vivo* studies have established the emollient and keratolytic properties of urea. Common study endpoints include reduction of TEWL, stratum corneum hydration, and clinical assessment. Urea has been shown to change certain physical properties of the skin. Early studies have shown that urea can induce conformational changes in proteins by causing unfolding, solubilization, and denaturation [73]. By possibly breaking hydrogen bonds and interfering with the quaternary structure of keratin, urea disperses and denatures keratin without disrupting the epidermal water barrier [26,74]. Several studies have also shown that urea decreases the DNA synthesis index of epidermal cells, leading to a thinning of the epidermis and reduction of basal epidermal cells. An early hypothesis was formed that pretreatment or concomitant treatment with urea can enhance efficacy of other topical therapies [75–77]. Salicylic acid is frequently combined with urea to produce a significant keratolytic effect [78]. Urea can enhance debridement in vascular and diabetic ulcers [69]. Studies investigating the emollient/keratolytic effects of urea in different skin conditions are outlined in Table 8 [14,16,33,40,41,78–85].

Table 8. Clinical studies of the emollient/keratolytic effects of urea

Skin Type	Test Agent	Comparison Agent	N	Study design	Treatment Protocol	Results	Safety (N)*	Year	Reference
Healthy	40% urea in canola oil	Drug-free vehicle	78	CT BL	BID x 7 weeks	Test agent increased TEWL after long term exposure	No adverse effects noted	2007	[80]
Healthy	5% ammonium lactate with 3 or 5% urea	Drug-free vehicle	22	CT	BID x 7 days and then SLS irritant applied TID x 1 day	Test agents improved stratum corneum hydration and barrier function	No adverse effects reported	2002	[79]
Healthy	40% urea with salicylic acid	None	20	OL	Single application	Test agent proven keratolytic using the silver nitrate test	No adverse effects reported	2001	[78]
Healthy	10% urea + 2% salicylic acid.	None	10	OL	Single exposure followed by removal by adhesive tape	The degree of stratum corneum removal was not increased after 6h exposure to test agent	No adverse effects reported	1995	[81]
Healthy	Moisturizers with varying urea content	Urea-free vehicle	26	CT	Single application	Test agents are very potent skin humidifier and descaling agent	No adverse effects reported	1992	[40]
Healthy	10% urea/5% lactic acid/4.3% betaine (ULB); 10% urea alone	Base ointment	5	CT	QD up to 6 days	Only ULB cream showed penetration at days 3 and 6	No adverse effects noted	1989	[82]
Healthy	5% salicylic acid with 10% urea ointment	5% and 10% salicylic acid alone	6	CT	Single 4-hour application on back skin	Test agent had increased keratolysis than 5% salicylic acid	No adverse effects noted	1987	[83]
Hyperkeratotic	30% urea emollient foam	None	10	CS	BID x 4 weeks	Significant improvements in skin condition and patients' ratings of quality of life	No adverse effects noted	2008	[84]
Psoriatic	10% urea cream	None	20	OL	Observed 2h after application	Test agent improved stratum corneum hydration, water-binding capacity, and TEWL	No adverse effects reported	1989	[41]

Various	10% and 20% urea with and without 1% hydrocortisone	None	158	OL	BID x 8 weeks	Test agents moisturizes and promotes penetration of hydrocortisone	Irritation (2), flared stasis ulcer (2)	1990	[85]
Xerotic	10% urea cream	12% ammonium lactate	36	CT BL	BID x 3 weeks	Test agent lowered TEWL and dryness	No adverse effects reported	1998	[33]
Xerotic	10% urea	None	10	OL	QD x 2-4 weeks	Test agent reduced chapping and scaling of skin	No adverse effects reported	1989	[14]
Xerotic	10% urea cream	1% hydrocortisone cream	14	CT BL	BID x 2 weeks	Improved with: urea (4), comparison (2), and no difference (7)	No adverse effects reported	1969	[16]

Abbreviations: CT - controlled trial, OL - open label, CS – case series, CR – case report, BL – bilateral comparison (test versus control), QD – daily, BID – twice daily, TID – thrice daily, TEWL – transepidermal water loss
*Safety profile is only reported for test agents containing urea.

Pruritus

There is limited evidence that topical urea application can improve symptoms of pruritus. An early study investigated the antipruritic effects of two urea solutions and their urea-free placebos. Patients with pruritic dermatoses received intradermal injections of trypsin as an irritant followed by a measurement of the duration of itch sensation. Thereafter, test or placebo solution was applied followed by a second round of trypsin injections and measurement of itch duration. The urea solutions provided a significant prophylactic antipruritic effect when compared to placebo in every case [86].

In a separate clinical study, 15 patients with pruritic dermatoses were asked to apply a urea solution to pruritic skin and instructed not to reuse the solution until itching returned. Pruritus resolved within minutes for the majority of patients and most patients expressed satisfaction with the antipruritic effect [86].

Chemical Nail Avulsion / Dystrophic Nails

Urea 40% has been used successfully under occlusion to achieve chemical avulsion of the nail in a number of studies. An early study with 35 patients showed that both 22% and 40% urea applied under occlusion could avulse nails in less than 10 days [87]. Non-dystrophic nails were not affected. Infrequent and transient side effects of maceration and irritation were reported. In onychomycosis, once the dystrophic nail is removed, subsequent treatment with topical antifungal drugs is facilitated. The failure to achieve avulsion is usually owing to lack of gross nail dystrophy, inadequate occlusion of the dressing, water immersion by the patient, and/or the use of an outdated urea preparation. Benefits of chemical over surgical avulsion include decreased risk of bleeding and infection as well as enhanced function [88].

Penetration Enhancement

A number of studies support the capacity of urea to enhance penetration of drug substances into the skin. A variety of substances have been studied, including topical steroids and topical antifungal drugs. Urea is thought to alter the physical and chemical properties of keratin, enhancing permeation of mono-substances. Urea can also alter the permeation kinetics of the horny layer of the skin by changing the binding capacity, leading to decreased penetration and increased retention time [89].

Many studies have looked at the concomitant use of urea in topical steroid application. An early study assessed the penetration of topical cortisol in four different vehicles: 10% urea in a cream base, 10% urea in a stabilizing emulsified base, and two control creams. The skin of a pig was used. The urea-cream base penetrated the skin with a 30-fold increase in efficacy compared to the emulsified base [90]. A second study found that 10% urea increases the penetration of hydrocortisone and triamcinolone acetonide by 50%, increasing the therapeutic effect of the drugs [91]. A third study used a powder-cream base containing a hyperosmolar urea solution absorbed in starch granules, suspended within a continuous lipid phase of an aqueous-lipid emulsion incorporating 1% hydrocortisone. When tested in adults, the vehicle increased efficacy and increased penetration of hydrocortisone, producing an effectiveness comparable to that of 0.1% betamethasone-17-valerate [44]. An *in vitro* study using guinea pig skin, however, showed that 10% urea decreased the percutaneous absorption of hydrocortisone [92].

Conclusion

Urea has been used safely and effectively in large populations of patients across a wide variety of disease settings. Urea is moisturizing and keratolytic, making it useful in diseases of dry and scaly skin such as ichthyosis, xerosis, and psoriasis. Urea enhances skin penetration and overall clinical benefit of other drugs such as corticosteroids and antifungals when used concomitantly. Urea therapy has been associated with few adverse effects and is generally well tolerated. Both the safety and efficacy of urea have been largely established over the past hundred years and urea should continue to be considered by clinicians as a viable treatment option for patients**.**

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